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EXAMINER	
SHTERENGARTS, SAMANTHA L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,575	DAVIDSON ET AL.	
	Examiner	Art Unit	
	SAMANTHA SHTERENGARTS	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☒ Claim(s) *24 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12 October 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-30 are currently pending in the instant application.

Priority

2. The instant application is a national stage entry of PCT/GB2004/001831, filed April 29, 2004, which claims the priority of Great Britain Patent Application No. 0310056.7, filed May 1, 2003.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on October 12, 2005 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS was considered. A signed copy of form 1449 is enclosed herewith.

Claim Objections

4. **Claims 24 and 30** are objected to because of the following informalities: The word "dependant" is used as an adjective to describe dependency of a disease. In this context, it appears that the word is misspelled and should be spelled, "dependent." The disorder "distonia" appears to be misspelled. The correct spelling is "dystonia." Also, the first letter of the word "the" in claim 24 should be capitalized. Claims should begin with a capital letter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

(First Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

5. **Claims 1-30** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of the Formula (I) and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for prodrugs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and, concomitantly, to use the invention commensurate in scope with these claims.

The Nature of the Invention

Claims 1-30 are drawn to a compound of the Formula (I) or a prodrug thereof, a pharmaceutical composition comprising that prodrug, a process for preparing a medicament for the treatment of various disorders comprising that prodrug, and a method of treating various diseases comprising that prodrug. Finding a prodrug is an empirical exercise. Predicting, e.g., if a certain compound is in fact a prodrug that produces the active compound metabolically at a therapeutic concentration and a useful rate, is filled with experimental uncertainty. Attempts have been made to predict drug metabolism *de novo,* but this is still an experimental science. A prodrug of a compound must meet three tests. It must itself be biologically active. It must be metabolized to a second substance *in vivo* at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria requires a clinical trial setting and a large quantity of experimentation.

The State of the Prior Art

"Pro-drugs" are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized in vivo into an active metabolite. As disclosed in Stella (Expert Opinions *Prodrugs as therapeutics*), "prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism, and targeting limitations" (277). Stella, Valentino J, Expert Opinion of

Therapeutic Patents, *Prodrugs as therapeutics*, 2004 14(3): 277-280. Wolff et al. (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pgs. 975-977, 1994) summarizes that state of the prodrug art, the lengthy research involved in successfully identifying a prodrug, and difficulties of extrapolating between species. With the limited direction and exemplification the specification offers, it is highly unpredictable that the compounds of Formula (I) will actually form effective prodrugs. The evidence supports the conclusion that the method of making claimed prodrugs is a subject for further study and experimentation.

The Level of Skill in the Art and the Predictability or lack thereof in the art

The level of skill of the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities as prodrugs. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any prodrug on its face, without evidence to support that particular prodrug. It is noted that the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Thus, the more unpredictable the art, the more information in support of the invention is required to satisfy the statute. See *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Each embodiment of a prodrug must be support by this invention in order to be enabled for the full range of prodrugs of compounds of the Formula (I).

The Amount of Direction or Guidance Present

The specification discloses in ¶ [0229], "the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I). For example, the compound of formula (I) may be prepared in a prodrug form wherein a free --OH group is derivatised (for example, via an ester, amide or phosphate bond) with a suitable group (the group may contain, for example, an alkyl, aryl, phosphate, sugar, amine, glycol, sulfonate or acid function) which is suitably labile so as it will be removed/cleaved (e.g. by hydrolysis) to reveal the compound of formula (I) sometime after administration or when exposed to the desired biological environment." This disclosure is directed to *any* pharmaceutically acceptable prodrug; however, as discussed above, it would be necessary for Applicant to provide evidentiary support for each embodiment due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others. Additionally, the examples in the specification are not sufficient to enable one skilled in the art to which it pertains to make and use *any* pharmaceutically acceptable prodrug as defined in the specification. There are no working examples drawn to prodrugs of compounds of the Formula (I) as claimed. The specification does not adequately enable a method of making all prodrugs of the compounds that the claims encompass. The specification has limited exemplification thereof and of the necessary starting materials, as discussed *supra*.

As stated in Morton International Inc. v. Cardinal Chem, Co., 28 USPQ2d 1190:

> [T]he specification purports to each, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However... there is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds..., there is...no evidence that such compounds even exist.
>
> The same circumstance is true here.

The Breadth of the Claims

The claims are drawn to *any* pharmaceutically acceptable prodrug of the compound of Formula (I). As discussed above, this broad disclosure cannot possibly enable one skilled in the art to which it pertains to make and use *any* pharmaceutically acceptable prodrug due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others.

The specification provides limited support, as noted above, for the large number of prodrugs encompassed by the claims. The quantity of experimentation needed to make and use all of the prodrugs encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons state above. Even with the undue burden of experimentation, there is no guarantee that one would obtain the desired prodrugs in view of the Wolff reference.

This discussion established *prima facie* non-enablement. Cancellation of "prodrug" from the claims would overcome this rejection.

The Quantity of Experimentation Needed

Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the pertinent art would be burdened with undue experimentation study to determine whether *any* pharmaceutically acceptable prodrug of compounds of the Formula (I) would successfully act as prodrugs as they are known in the art. Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which

prodrugs, if any, would produce desired activity with compounds of the Formula (I), with no assurance of success.

6. **Claims 21-30** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc.; that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

I. Scope of Claims

Claims 21-30 are drawn to a process for preparing a medicament for the treatment of a disorder "mediated by" CB_1 receptors and a method of treatment of a disorder "mediated by" CB_1 receptors. The diseases that are indicated for the treatment involving CB_1 receptors include

a majority of central nervous system disorders. These diseases vary in the way that they interact with receptors. It is unclear as to what "mediated by" means in these claims. When receptors are involved with the treatment of diseases, they can be acting in various ways to inhibit, antagonize, or bind.

II. Scope of Disclosure

Reduction to Practice

The specification does not provide a proper written description to allow one of ordinary skill in the art to properly ascertain what the involvement is between the receptor and the disease. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, Applicant claims a process for preparing a medicament for the treatment of a disorder mediated by CB_1 receptors (claim 21) and a method of treatment of a disorder mediated by CB_1 receptors (claim 22). However, there is no written description of the phrase "mediated by" such that one of ordinary skill in the art would reasonably discern the meaning of this phrase. The specification does not describe, or even mention, the degree to which the mediation of the disorder by CB_1 receptors needs to take place.

III. Analysis of Fulfillment of Written Description Requirement:

The structure/activity relationship for activity is elucidated upon analysis of the process for preparing a medicament for the treatment of a disorder mediated by CB_1 receptors (claim 21) and the method of treatment of a disorder mediated by CB_1 receptors (claim 22). There are numerous

ways that CB_1 receptors can be "mediated" in relation to the specific disease that is involved. These receptors can be inhibited, they can be bound, and most commonly in the instant case, they can be antagonized as discussed in the prior art. There is insufficient written description to support *mediation* without further explanation of the diseases that are being mediated and the type of mediation occurring in relation to each disease. Without further guidance from the instant disclosure, it is not possible to determine what is meant by "mediated by" that would allow for the preservation of the desired activity.

The MPEP states:

> "[T]he essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998). "The written description requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). Further, the written description requirement promotes the progress of the useful arts by ensuring that patentees adequately describe their inventions in their patent specifications in exchange for the right to exclude others from practicing the invention for the duration of the patent's term.

In conclusion, the disclosure of the instant application is insufficient in adequately describing the definition of "mediated by," as it related to the diseases which are being affected and in what manner they are being affected. Thus, the specification fails to provide adequate written description and does not reasonably convey to one skilled in the pertinent art that the

inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Applicant has also claimed a method wherein the disorder is a gastrointestinal disorder (claims 24 and 29). Gastrointestinal disorder is a broad term encompassing many different diseases. The present disclosure fails to recite any physical characteristics of a gastrointestinal disorder such that the artisan would readily identify the scope of this disorder. In specification ¶ [0225], there is an example of certain gastrointestinal disorders; however, examples to not encompass each embodiment of gastrointestinal disorders as instantly claimed. Because there is no support in the disclosure for the phrases "mediated by" and "gastrointestinal disorder," it is not clear that applicant had possession of the claimed invention at the time of filing.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See Fiers v. Revel, 25USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18USPQ2d 1016.

7. **Claims 22-30** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of some eating disorders associated with excessive food intake, does not reasonably provide enablement for the treatment and

prophylactic treatment of the long list of disorders encompasses by instant claim 24 and subsequent dependent claims, or for all diseases in which CB1 receptors are involved. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Nature of the Invention

Claims 22-30 are drawn to a method of treating and preventing (prophylactic treatment) of a disorder mediated by CB_1 receptors wherein the disorder is selected from psychosis, memory deficit, cognitive disorders, attention deficit disorder, migraine, neuropathy, neuro-inflammatory disorders, cerebral vascular injuries, head trauma, anxiety disorders, depression, stress, epilepsy, dementia, distonia, Alzheimer's disease, Huntingdon's disease, Tourette's syndrome, ischaemia, pain, Parkinson's disease, schizophrenia, substance abuse disorders, smoking cessation, treatment of nicotine dependence and/or treatment of symptoms of nicotine withdrawal, gastrointestinal disorders, eating disorders associated with excessive food intake, and non-insulin dependant diabetes mellitus.

As defined in ¶ [0228] of the specification, "the term "treatment" as used herein includes prophylactic treatment." The prophylactic treatment or "prevention" actually means to anticipate or counter in advanced, to keep from happening, etc. and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds, compositions, and medicaments can be administered in order to have the "preventative" effect.

The State of the Prior Art and the Predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instantly claimed invention is highly unpredictable as discussed below: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects of the above listed diseases, whether or not the disease is affected by the instantly claimed compounds.

Applicants are claiming products with intended uses which include the treatment and prevention (prophylaxis) of various diseases such as psychosis, including, but not limited to: mood disorders, depression, schizophrenia, delusions, bipolar disorder, sleep deprivation, as well as other diseases such as attention deficit disorder, Parkinson's disease, substance abuse disorders, in addition to central nervous system disorders such as epilepsy, pain, and anxiety.

With regards to products for the treatment and prevention of psychosis, which is defined as a *generic* psychiatric term for a mental state often described as involving a "loss of contact with reality," these disorders embrace a vast array of problems. Thus, it covers Schizophrenia,

Schizoaffective disorder, and Schizophreniform disorder. It covers various types of brief psychotic disorders such as delusions and sleep deprivation. It covers various types of depression, such as, bipolar disorder (manic depression) and severe clinical depression for example. Another embodiment of psychosis is severe psychosocial stress. Additionally, there is another class of psychotic conditions that stem from organic conditions, also known as, secondary psychosis. Some of these neurological disorders include brain tumors, dementia, multiple sclerosis, syphilis, and Alzheimer's disease. Some of these electrolytic disorders include hypoalcemia, hypermagnesemia, lupus, AIDS, leprosy, and malaria. Not one compound, or any set of derivatives of a compound, could possibly be effective against such disorders, especially since some of these are currently not treatable, and certainly not preventable.

With regards to products for the treatment and prevention of various eating disorders associated with excessive food intake, which by definition *can* include cardiovascular disorders, these disorders embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis, elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, pulmonary hypertension, etc. Not one compound, let alone a genus of compounds, could possibly be effective against such disorders generally.

With regards to products for the treatment and prevention of non-insulin dependent diabetes mellitus, various embodiments of this disease are described as follows. Diabetes

(diabetes mellitus) is defined as impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia. Early symptoms are related to hyperglycemia and include polydipsia, polyphagia, and polyuria. Later complications include vascular disease, peripheral neuropathy, and predisposition to infection. There are two main categories of diabetes: mellitus type I and type II. Treatment involves control of hyperglycemia to improve symptoms and prevent complications while minimizing hypoglycemic episodes. Oral antihyperglycemic drugs are the primary treatment for type II diabetes mellitus. However, there are no treatments that definitely prevent the onset or progression of type I diabetes mellitus. In addition to the limited treatment, there is no cure for diabetes.

http://www.merck.com/mmpe/print/sec12/ch158/ch158b.html

With regards to products for the treatment and prevention of cognitive disorders, there are various classifications for all cognitive disorders. There are social cognitive disorders, which include attention deficit disorder, Asperger's syndrome, and autism; there are neurological cognitive disorders, such as delirium, multi-infarct dementia, dementia associated with alcoholism, dementia, as well as neuropathies, such as neuropathy (pain) and neuro-inflammatory diseases. In terms of autism, there is no single treatment protocol for all children with autism, but most individuals respond best to highly structured behavioral programs. One of the claimed disorders, dementia, as defined by Medline Plus, is word for a group of symptoms caused by disorders that affect the brain. It is not a specific disease. Right now, dementia related diseases are not preventable. In terms of attention deficit disorder, Medline Plus discussed how "No one knows exactly what causes ADHD." One of ordinary skill in the art cannot be enabled to treat and prevent this disorder when there is not a known cause.

http://www.nlm.nih.gov/medlineplus/dementia.html#cat5

http://www.nlm.nih.gov/medlineplus/autism.html

http://www.nlm.nih.gov/medlineplus/attentiondeficithyperactivitydisorder.html#cat3

With regards to products for the treatment and prevention of substance abuse disorders, there is also not just one type of substance abuse disorder. As with the disorders discussed above, there are many substance abuse disorders that must be treated and/or prevented in different manners. Some of the common substance abuse disorders known in the art are alcohol dependence, amphetamine dependence, cannabis dependence, cocaine dependence, hallucinogen dependence, inhalant dependence, nicotine dependence, and sedative dependence. For many of these dependencies, withdrawal is considered a form of treatment, sometimes without medication, as well as community and family support.

With regards to products for the treatment and prevention of anxiety, there are also various disorders that fall within this category. Anxiety encompasses acute stress disorder, panic disorder, social phobic, obsessive compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, stress, and depression. Anxiety has various treatments, the most common of which is cognitive therapy.

http://www.nlm.nih.gov/medlineplus/anxiety.html#cat3

With regards to products for the treatment and prevention of central nervous system disorders, such as the majority of the list in claim 24, as well as disorders not yet discussed such as epilepsy, Huntington's disease, Tourette's syndrome, migraines, and Parkinson's disease, are

defined as disorders that affect the brain and the spinal cord. There is no prevention or cure for Parkinson's disease, but medication and, in some cases; surgery or stimulation directly on the brain can help relieve the symptoms. Epilepsy has many possible causes, including illness, brain injury and abnormal brain development. In many cases, the cause is unknown.

http://www.nlm.nih.gov/medlineplus/epilepsy.html

http://www.nlm.nih.gov/medlineplus/parkinsonsdisease.html

Since Claims 22-30 are drawn to methods of treating disorders mediated by CB_1 receptors, it is important to point out that there are various adverse effects have been reported between drugs that bind these receptors and anxiety and depression, among other central nervous system disorders. In the American Journal of Medicine, Jenson disclosed that cannabinoids (CBs) exert an anti-anxiety effect and that those patients who have a predisposition or an underlying serious anxiety disorder, as well as depressive symptoms, should be careful as it may increase the likelihood of central nervous system side effects without enhancing therapeutic effects.

Hence, in the absence of a showing of correlation between all of the aforementioned diseases claimed as capable of treatment or prevention by the compound of claim 1, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role the instantly claimed compound.

The amount of direction or guidance present and the presence or absence of working examples

The specification discloses various binding data for CB_1 receptors *in vitro*, as well as the regulation of feeding behavior *in vivo* that supports the scope of enablement for some disorders

that are associated with excessive food intake, such as reducing food intake and body weight, as disclosed in Carai et al. (CNS Drug Reviews). However, the specification does not contain any evidentiary support or working examples to support the treatment or prevention of the other disorders contained in claim 24.

The breadth of the claims

The claims are drawn to a method of treatment of a disorder "mediated by" CB_1 receptors wherein the disorder is selected from claim 24. Since treatment has been defined in the specification as treatment and prophylaxis, the claims are drawn to the treatment and prevention of an entire class of central nervous system disorders. Not one compound, let alone a genus of compounds, could possibly be effective against such disorders generally.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases, out of all diseases, would be benefited (treated or prevented) by the compounds and compositions of Formula I and would furthermore have to determine which of the claimed compounds would provide treatment or prevention of which disease.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the inventions is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compound exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment or prevention of the various diseases, as a result necessitating one of skill to perform an exhaustive search for which diseases can be treated or prevented by what compounds of the instant claims in order to practice the claimed invention. Only a majority of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not mean that the other diseases meet the enablement requirements.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. nave been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the diseases that are not enabled within the method claims.

(Second Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. **Claim 24, 28, and 30** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 contains the phrase "memory deficit" within the list of disorders as claimed to be treated and prevented by the compounds of Formula (I). "Memory deficit" is not known in the art as a disorder. Memory deficit is defined as a lack or impairment in function capacity of the memory, based on the combined definition of these two words. It is unclear what disorder related to deficient memory Applicant regards as the invention being claimed. Claims 24, 28, and 30 contain the phrase "smoking cessation" within the list of disorders as claimed to be treated and prevented by the compounds of Formula (I). "Smoking cessation" is defined as quitting smoking. This is not a disorder and it is unclear what Applicant regards as the invention being claimed.

http://www.nlm.nih.gov/medlineplus/smokingcessation.html

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. **Claims 1-30** are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al. (WO 99/37612) in view of Achard et al. (US 2002/0019383).

Determination of Scope and Contents of the Prior Art

WO 99/37612 discloses positional isomers of the instantly claimed compounds.

Ascertaining the differences between the prior art and the claims at issue

Instant claims 1-19 are drawn to compounds of the Formula (I) wherein at least one of R^1 and R^2 has a non-hydrogen substituent in the ortho-position(s) thereof relative to the point of attachment to the –C-H-O- group. WO 99/37612 discloses many compounds that are positional isomers of the instantly claimed compounds. On page 21, example 13, is a positional isomer of instant claims 1-6, 9, and 13. The chlorine (halogen) atoms are located at the meta and para positions, rather than the ortho position. The aforementioned alternative changes would produce compounds which are encompassed by the genus of claim 1.

Instant claim 20 is drawn toward a pharmaceutical composition comprising a compound of the Formula (I) and a suitable excipient. Instant claims 21 is drawn toward a process for preparing a medicament for the treatment of a disorder mediated by Cb_1 receptors comprising

combining the compound according to claim 1 with a suitable excipient. It is obvious to add a carrier to an obvious compound. Ex parte Douros, 163 USPQ 667 (1968).

Instant claims 22-30 are drawn to a method of treatment of a disorder mediated by CB_1 receptors comprising administration of a compound of Formula (I) to a subject in need of such treatment wherein the disorder is selected from the list in claim 24. The instant application discussed compounds of the Formula (I) that are obvious over Adams et al., as discussed above. These azetidine carboxamide derivatives are taught in Adams et al. as being used for the treatment of disorders of the central nervous system, such as anxiety, epilepsy, substance abuse disorders, etc. (Specification, page 7, last paragraph).

Adams et al. differs from the instant claims insofar as they do not teach that the compounds treat these disorders by interacting with cannabinoid (CB_1) receptors, or that the compounds can also treat obesity or gastrointestinal disorders.

Achard et al. teaches a method of the treating disorders of the central nervous system, such as anxiety, epilepsy, and weaning from alcohol and drug abuse etc. by administering azetidine carboxamide derivatives ¶ [0085]. "These compounds possess a high affinity for the cannabinoid receptors and particularly those of the CB_1 type. They are CB_1-receptor antagonists and are therefore useful in the treatment and prevention of disorders affecting the central nervous system, the immune system, the cardiovascular or endocrine system, the respiratory system, the gastrointestinal apparatus, and reproductive disorders" ¶ [0084]. Additionally, these azetidine carboxamide derivatives are also useful in treating obesity, and intestinal transit disorder (a gastrointestinal disorder) ¶ [0085].

Resolving the level of ordinary skill in the pertinent art – Prima Facie Case of Obviousness

One of ordinary skill would be motivated to make the positional modifications required to arrive at the instant invention with reasonable expectation for success of obtaining a compound that is active for the treatment of a central nervous system disorder or a disorder involving CB_1 receptor binding or antagonism. WO 99/37612 discloses an azetidinecarboxamide derivative for treating CNS disorders on page 21, example 13, which contains a fluorine atom in the ortho position as in the instantly claimed invention. Additionally, instant claim 4 shows that the substituents in question can be substituted on the aryl ring at variable points of attachment. None of the substituents of instant claim 4 are specifically designated at the ortho position; however, with three possible substituents, if 2 were occupying both ortho positions, at least one substituent would be located at either a meta or para position. It is obvious to one of ordinary skill to make this modification with reasonable expectation for success. The motivation to make this modification would be to make alternate compounds for the quoted purpose.

When chemical compounds have similar structural limitations and similar utilities, a *prima facie* case of obviousness may be made. *In re Wilder*, 563 F2d 457 (CCPA 1957). The necessary motivation to make the claimed compounds, and thus the prima facie case of obviousness, arises from the reasonable expectation that compounds similar in structure will have similar properties. *In re Gyurik*, 596 F2d 1012, 1018 (CCPA 1979). It would have been obvious to a person having ordinary skill in the art at the time of Applicant's invention to administer the compositions disclosed in Adams et al. for the treatment of obesity since similar azetidine carboxamide derivatives were known to treat obesity. The artisan would reasonably

expect the compounds of Adams et al. to bind CB_1 receptors and treat the same diseases as taught in Achard et al., since the compounds of Achard and Adams treat the same diseases and are both azetidine carboxamide derivatives.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. **Claims 1-30** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 18, and 21-24 of U.S. Patent No. 6, 403, 574 in view of Achard et al. (U.S. Patent No. 6,566,356).

Determination of Scope and Contents of Claims 1-15, 18, and 21-24 of US Patent No. 6,403,574

Claims 1-15, 18, and 21-24 of U.S. Patent No. 6,403,574 are drawn toward compounds of the Formula (I), which are positional isomers of the instantly claimed compounds, pharmaceutical compositions comprising a compound according to the Formula (I), and a method of treating CNS disorders comprising administering a compound of the Formula (I).

Ascertaining the differences between claims 1-15, 18, and 21-24 of US Patent No. 6,403,574 and the claims at issue in the instant application

Instant claims 1-19 are drawn to compounds of the Formula (I) wherein at least one of R^1 and R^2 has a non-hydrogen substituent in the ortho-position(s) thereof relative to the point of attachment to the –C-H-O- group. Claims 1-15 and 18 of U.S. Patent No. 6,403,574 disclose many compounds that are positional isomers of the instantly claimed compounds. On page 14, example 13, is a positional isomer of instant claims 1-6, 9, and 13. The chlorine (halogen) atoms are located at the meta and para positions, rather than the ortho position. The aforementioned alternative changes would produce compounds which are encompassed by the genus of claim 1.

Instant claim 20 is drawn toward a pharmaceutical composition comprising a compound of the Formula (I) and a suitable excipient. Claim 21 of U.S. Patent No. 6,403,574 discloses a

pharmaceutical composition comprising a compound of the Formula (I) with a pharmaceutically acceptable carrier or excipient. It is obvious to add a carrier to an obvious compound. Ex parte Douros, 163 USPQ 667 (1968).

Instant Claims 22-30 are drawn to a method of treatment of a disorder mediated by CB_1 receptors comprising administration of a compound of Formula (I) to a subject in need of such treatment wherein the disorder is selected from the list in claim 24. The instant application discussed compounds of the Formula (I) that are obvious over U.S. Patent No. 6,403,574, as discussed above. These azetidine carboxamide derivatives are taught in U.S. Patent No. 6,403,574 as being used for the treatment of disorders of the central nervous system, such as anxiety, epilepsy, substance abuse disorders, etc. (Specification, page 4, last paragraph).

U.S. Patent No. 6,403,574 differs from the instant claims insofar as they do not teach that the compounds treat these disorders by interacting with cannabinoid (CB_1) receptors.

U.S. Patent No. 6,566,356 teaches a method of the treating disorders of the central nervous system, such as anxiety, epilepsy, and weaning from alcohol and drug abuse etc. by administering azetidine carboxamide derivatives (page 10, first paragraph) "These compounds possess a high affinity for the cannabinoid receptors and particularly those of the CB_1 type. They are CB_1-receptor antagonists and are therefore useful in the treatment and prevention of disorders affecting the central nervous system, the immune system, the cardiovascular or endocrine system, the respiratory system, the gastrointestinal apparatus, and reproductive disorders" ¶ [0084]. Additionally, these azetidine carboxamide derivatives are also useful in treating obesity, and intestinal transit disorder (a gastrointestinal disorder) ¶[0085].

Resolving the level of ordinary skill in the pertinent art – Prima Facie Case of Obviousness

One of ordinary skill would be motivated to make the positional modifications required to arrive at the instant invention with reasonable expectation for success of obtaining a compound that is active for the treatment of a central nervous system disorder or a disorder involving CB_1 receptor binding or antagonism. Claims 1-15, 18, and 21-24 of U.S. Patent No. 6,403,574 disclose an azetidinecarboxamide derivative for treating CNS disorders on page 14, example 13, which contains a fluorine atom in the ortho position as in the instantly claimed invention. Additionally, instant claim 4 shows that the substituents in question can be substituted on the aryl ring at variable points of attachment. None of the substituents of instant claim 4 are specifically designated at the ortho position; however, with three possible substituents, if 2 were occupying both ortho positions, at least one substituent would be located at either a meta or para position. It is obvious to one of ordinary skill to make this modification with reasonable expectation for success. The motivation to make this modification would be to make alternate compounds for the quoted purpose.

When chemical compounds have similar structural limitations and similar utilities, a *prima facie* case of obviousness may be made. *In re Wilder*, 563 F2d 457 (CCPA 1957). The necessary motivation to make the claimed compounds, and thus the prima facie case of obviousness, arises from the reasonable expectation that compounds similar in structure will have similar properties. *In re Gyurik*, 596 F2d 1012, 1018 (CCPA 1979). The artisan would reasonably expect the compounds of Claims 1-15 and 18 of U.S. Patent 6,403,574 to bind CB_1 receptors and treat the same diseases as taught in U.S. Patent 6,566,356 since the compounds of

U.S. Patent 6,566,356 and U.S. Patent 6,403,574 treat the same diseases and are both azetidine carboxamide derivatives.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samantha Shterengarts whose telephone number is (571)270-5316. The examiner can normally be reached on Monday thru Thursday, 9AM – 6PM Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang and Janet Andres can be reached on 571-272-0562 and 571-272-0867, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAMANTHA SHTERENGARTS/

Examiner, Art Unit 4131

/Janet L. Andres/

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